UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/498,305	02/04/00	ENSLEY	B 2001605-0007

HM12/0716

Brenda Herschbach Jarrell
Choate Hall & Stewart
Exchange Place
53 State Street
Boston MA 02109

EXAMINER	
MOORE, W	
ART UNIT	PAPER NUMBER
1652	6

DATE MAILED: 07/16/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/498,305	ENSLEY, BURT D.
Examiner	**Art Unit**
William W. Moore	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-25 is/are pending in the application.

4a) Of the above claim(s) 20-22 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-19 and 23-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 & 5 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1652.

Information Disclosure Statement and Drawings

Applicant's submissions of Information Disclosure Statements, Papers Nos. 4 and 5 filed, respectively, April 11 and 21, 2000, is hereby acknowledged and the references applicant submitted are made of record on the accompanying forms PTO-892. A Notice of Draftsman's Patent Drawing Review, stating informalities requiring correction, accompanies this communication.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. §121:

I. Claims 1-19 and 23-25, drawn to a method of promoting wound healing comprising application of tropoelastin and lysyl oxidase and to a first kit comprising separate compartments for tropoelastin and lysyl oxidase, classified in class 424, subclass 94.4.

II. Claim 20, drawn to a second kit comprising tropoelastin and a convertibly inactivated form of lysyl oxidase in a single compartment, classified in class 424, subclass 94.3.

III. Claims 21 and 22, drawn to a third kit comprising tropoelastin and lysyl oxidase in a single compartment wherein either the tropoelastin or the lysyl oxidase is encapsulated by a polymer, classified in class 424, subclass 451.

Inventions of Group I and Group II are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP §806.05(c)). In the instant case, the combination of Group I as claimed does not require the particulars of the subcombination of Group II as claimed because it is entirely functional in the absence of a convertible oxidase inhibitor. The subcombination has separate utility such as cosmetic application.

Inventions of Group I and Group III are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP §806.05(c)). In the instant case, the combination of Group I as claimed does not require the particulars of the subcombination of Group II as claimed because it is entirely functional in the absence of encapsulated enzyme or encapsulated substrate. The subcombination has separate utility such as parenteral administration.

Inventions of Group II and Group III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP §806.04, MPEP §808.01). In the instant case the different inventions are not disclosed to be capable of concurrent use and have different modes of operation.

During a telephone conversation with Ms. Brenda Jarrell on July 18, 2000, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-19 and 23-25. A restriction requirement as among species of recombinantly-modified or unmodified tropoelastin, and recombinantly-modified or unmodified lysyl oxidase, used in a claimed method was also stated, and an election made in the conversation but this requirement is hereby rescinded. Affirmation of this election must be made by applicant in replying to this Office action. Claims 20-22 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention and claims 1-19 and 23-25 are examined herein.

Claim Objections

Claims 1 and 12 are objected to because of the following informalities: The grammar of claim 1 is defective where, at line 2, an "isolated tropoelastin" is required by the

context and were, at line 4, the word "wound" lacks an indefinite article. Claim 12 states "claims" at line 1 yet refers to only a single claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 6-8, 16, 18 and 19 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 3, 5 and 15 are not subject to this rejection because, while the specification does not disclose their preparation, Applicant is considered to have been in constructive possession of certain tropoelastin substrates that may be utilized in claimed methods other than full-length, native, tropoelastins where the specification both discusses and references tropoelastins that are isoforms either arising from alternative splicing or by manipulation of cloned, tropoelastin-encoding nucleic acid sequences and then recombinantly-produced to generate a natural isoform. The specification fails, however, to exemplify, describe or discuss the location(s) for modification of the amino acid sequence of a tropoelastin substrate contemplated by claims 4 and 16. The specification also fails to exemplify, describe or discuss the location(s) for modification of the amino acid sequence of a lysyl oxidase enzyme of claims 6-8, 18 and 19 and does not otherwise disclose or suggest the nature or source of a modified lysyl oxidase that meets the claim limitations. Only native full-length tropoelastins and isoforms and their recombinantly-produced counterparts are specifically taught by the specification, which provides no teaching of a truncated enzyme of claim 6, nor a chemically modified enzyme of claims 7 and 18, nor a recombinantly-altered enzyme of claims 8 and 19. "While one does not need to have carried out one's

invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification contains no relevant identifying characteristics of any modified form of lysyl oxidase that functions in a claimed method, or is included in a claimed kit.

The Court of Appeals for the Federal Circuit held that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Even if Applicant had disclosed or suggested "a method for obtaining" a modified lysyl oxidase having the ability to function as claimed, or a tropoelastin modified by one or more amino acid substitutions deletions or insertions, nothing demonstrates that he was "able to envision" enough of the "structure of the" claimed product to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The specification's treatment of the claimed methods utilizing substrates with amino acid sequences differing from the native full-length tropoelastins and there naturally-arising isoforms, as well as its treatment of their truncated, chemically-modified, or recombinantly-modified lysyl oxidases is thus entirely prospective and skilled artisans in the relevant field molecular biology could not predict the structure of these products, the claimed methods of use thereof, or kits comprising them.

Claims 1-19 and 23-25 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a methods **of promoting healing of skin wounds** utilizing am unaltered **native**, or recombinantly-produced, exogenous or endogenous, **lysyl oxidase** and utilizing a **native**, exogenous or endogenous tropoelastin as well as recombinantly-produced **tropoelastin isoforms having amino acid sequences encoded by exons of the human and bovine tropoelastin genes**, and for kits comprising same,

does not reasonably provide enablement for methods of promoting wound healing in an artery or in lung tissue, or for methods utilizing a truncated lysyl oxidase or a lysyl oxidase having amino acid sequence alterations, or kits comprising same, or for methods utilizing a tropoelastin having an amino acid sequence that differs from that encoded by the exons of the human and bovine tropoelastin genes by one or more amino acid substitutions, deletions and insertions, or combinations thereof, at regions encoded by internal regions of exons, or kits comprising same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 2, 9-14, 17 and 23-25 are included in this rejection because they include subject matters of modified substrates and/or enzymes of claims 3-8, 15, 16, 18 and 19, dependent from claims 1 and 13 thus contemplate arbitrary assignments of any number of amino acid substitutions, additions or deletions in a tropoelastin substrate or a lysyl oxidase enzyme. Neither the specification nor the prior art supports modification of any portion of the amino acid sequences of native lysyl oxidases, nor any insertions, deletions, or substitutions anywhere, in any combination or any pattern, in amino acid sequences of tropoelastins other than those resulting from alternative splicing among and within exons or produced by selective exon deletion. The prior art made of record herewith is evidence, see, e.g. Parks et al., that no teaching in the relevant arts of protein engineering and molecular biology can be combined with the specification's disclosure to support the contemplated alteration of tropoelastin and lysyl oxidase acid sequences. Mere sequence perturbation cannot enable the design and preparation of nucleotide sequences encoding a myriad of divergent tropoelastins and lysyl oxidases yet provide the public with nucleotide sequences encoding either a substrate or an enzyme that retains its native function.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230

USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The standard set by the CCPA is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with degree of unpredictability of factors involved in physiological activity of small peptide hormone); see also, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (equivalency of divergent gene products unsupported where only a single B-cell growth factor allele disclosed). The Federal Circuit approved the CCPA's standard in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997).

The Federal Circuit has also considered whether definitional statements might enable a claim scope argued to extend beyond a disclosed gene product having its native amino acid sequence to embrace a specific variant gene product encoded by a specifically-altered DNA sequence. *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 31 USPQ2d 1161 (Fed. Cir. 1994). The court held that only a narrow structural and functional definition was enabling precisely because the sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent. *Genentech*, 29 F.3d 15 at 1564-65, 31 USPQ2d at 1168. Applying the "*Forman*" factors discussed in *Wands*, **supra**, to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for altering DNA sequences coding for, and encoded amino acid sequences of, a native lysyl oxidase or the exon-encoded amino acid sequences specified by tropoelastin genes,

b) the specification lacks working examples wherein DNA sequences coding for, and encoded amino acid sequences of, a native lysyl oxidase or the exon-encoded amino acid sequences specified by tropoelastin genes, are altered,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no lysyl oxidases, or internal regions or tropoelastins specified by exons of tropoelastin genes, have yet been identified for concurrent modification.

Thus the broad scope of the subject matters embraced by the phrases, "modified", "changed relative to amino acid sequences of the wild-type", and "enzymatically active portion of" is considered to be unsupported by the present specification, even if taken in combination with the teachings available in the prior art. This rejection may be overcome by limiting the subject matters as indicated in the statement at page 7, lines 24-29, above.

Allowable Subject Matter

Claims 1-19 and 23-25 are allowable over the prior art of record because claims 1 and 13 require that the tropoelastin substrate and lysyl oxidase be maintained apart from each other until applied. If the elected claims were amended to overcome the rejections above under the first paragraph of 35 U.S.C. §112, all would be allowed. Even though the role of the enzyme in cross-linking the substrate to form elastic fibrils in dermal and other tissues has been known for three decades and even though the native nucleotide coding sequences - indeed the genes of several vertebrate species - for both the enzyme and the substrate have been known for a decade, the closest prior art, Ensley et al.('040), supplied with Applicant's Information Disclosure, teach only that recombinantly-produced tropoelastin should be applied in methods of treating wounds and make no mention of joint or separate lysyl oxidase application. The further prior art made of record herewith - Capello, Weiss et al., Bell et al.('872), and Bell et al.(558) cited on the accompanying PTO Form 892 - teaches away from a claimed method by instructing the artisan to cross-link elastin fibrils by enzymatic - or chemical - activity **before** elastin, or tropoelastin, is to be applied to a wound site or to the skin. This marked trend in the art teaches away from the selection of tropoelastin, or its isoforms, as a component in a method wherein it is applied to a wound to promote healing separately from application of lysyl oxidase to the wound in the method.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached from 8:00AM-6:30PM EST on Mondays, Wednesdays, and Fridays and from 11:30AM-6:00PM EST on Tuesdays and Thursdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
July 2, 2001

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600